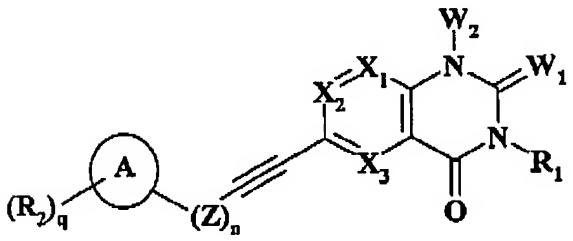
LISTING OF THE CLAIMS

The following listing of claims will replace all prior versions, and listings, of claims in the application.

Listing of claims:

1 (currently amended). A combination, comprising valdecoxib, or a pharmaceutically acceptable salt thereof, and an allosteric alkyne inhibitor of MMP-13 of Formula (A)



(A)

or a pharmaceutically acceptable salt thereof, or an N-oxide thereof,

wherein:

W_1 is O, S, or NR_3, wherein R_3 is hydrogen, $(C_1$-$C_6)$alkyl, hydroxyl or cyano;

W_2 is selected from:

hydrogen;

trifluoromethyl;

NH_2;

$(C_1$-$C_{10})$alkylN(H);

$[(C_1$-$C_{10})$alkyl$]_2$N, wherein each $(C_1$-$C_{10})$alkyl moiety is the same or different;

$(C_1$-$C_6)$alkyl;

$(C_3$-$C_6)$alkenyl;

$(C_3$-$C_6)$alkynyl;

phenyl;

naphthyl;

phenyl-$(C_1$-$C_{10})$alkyl;

naphthyl-$(C_1$-$C_{10})$alkyl;

$(C_3$-$C_{10})$cycloalkyl-$(C_1$-$C_{10})$alkyl;

an aromatic 5-membered or 6-membered monocyclic heterocycle comprising carbon atoms and from 1 to 4 heteroatoms selected from O, S, N(H), and N-$(C_1$-$C_{10})$alkyl;

a nonaromatic 5-membered or 6-membered monocyclic heterocycle comprising carbon atoms and from 1 to 3 heteroatoms selected from O, S, N(H), and N-$(C_1$-$C_{10})$alkyl;

wherein in W_2 each $(C_1$-$C_{10})$alkyl, $(C_1$-$C_6)$alkyl, $(C_3$-$C_6)$alkenyl, $(C_3$-$C_6)$alkynyl, phenyl, naphthyl, phenyl-$(C_1$-$C_{10})$alkyl, naphthyl-$(C_1$-$C_{10})$alkyl, $(C_3$-$C_{10})$cycloalkyl-$(C_1$-$C_{10})$alkyl, aromatic heterocycle, and nonaromatic heterocycle group is independently unsubstituted or substituted by from 1 to 3 groups, which may be identical or different, selected from halo, NH_2, $(C_1$-$C_{10})$alkylN(H), $[(C_1$-$C_{10})$alkyl$]_2$N, wherein each $(C_1$-$C_{10})$alkyl moiety is the same or different, cyano, trihalo$(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$acyl, C(=O)OR_4, -OR_4, and SR_4;

R_4 is hydrogen or $(C_1$-$C_6)$alkyl; ~~or~~

~~W_2 and W_1 may be taken together to form a diradical group W_2-W_1 of formula~~

~~W_3=X_4-N;~~

~~W_3 is N or CR_5 wherein R_5 is selected from:~~

~~hydrogen;~~

~~OR_6;~~

~~SR_6;~~

~~$(C_1$-$C_6)$alkyl;~~

~~$(C_3$-$C_8)$cycloalkyl;~~

~~a saturated heterocycle comprising from 3 to 8 ring members which are carbon atoms and one heteroatom selected from O, S, N(H), and N-$(C_1$-$C_{10})$alkyl;~~

~~phenyl;~~

~~naphthyl;~~

~~$(C_5$-$C_{10})$heteroaryl comprising carbon atoms and from 1 to 4 heteroatoms selected from O, S, N(H), and N-$(C_1$-$C_{10})$alkyl;~~

~~phenyl-$(C_1$-$C_{10})$alkyl; and~~

~~naphthyl-$(C_1$-$C_{10})$alkyl;~~

~~R_6 is selected from hydrogen, (C_1-C_6)alkyl, phenyl (C_1-C_{10})alkyl, and naphthyl (C_1-C_{10})alkyl;~~

~~wherein in W_3 each (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, saturated heterocycle, phenyl, naphthyl, (C_5-C_{10})heteroaryl, phenyl (C_1-C_{10})alkyl, and naphthyl (C_1-C_{10})alkyl group is independently unsubstituted or substituted by $(CH_2)_p$-OH or $(CH_2)_p$ NH_2;~~

~~p is an integer of from 0 to 4 inclusive;~~

~~X_4 is N or CR_7, wherein R_7 is selected from:~~

~~hydrogen;~~

~~NR_8R_9;~~

~~OR_8;~~

~~SR_8;~~

~~(C_1-C_6)alkyl;~~

~~(C_3-C_8)cycloalkyl;~~

~~a saturated heterocycle comprising from 3 to 8 ring members which are carbon atoms and one heteroatom selected from O, S, N(H), and N (C_1-C_{10})alkyl;~~

~~phenyl;~~

~~naphthyl;~~

~~(C_5-C_{10})heteroaryl comprising carbon atoms and from 1 to 4 heteroatoms selected from O, S, N(H), and N (C_1-C_{10})alkyl;~~

~~phenyl (C_1-C_{10})alkyl; and~~

~~naphthyl (C_1-C_{10})alkyl;~~

~~R_8 and R_9 are the same or different, and are selected from hydrogen; (C_1-C_6)alkyl; phenyl (C_1-C_{10})alkyl; and naphthyl (C_1-C_{10})alkyl;~~

~~wherein in X_4 each (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, saturated heterocycle, phenyl, naphthyl, (C_5-C_{10})heteroaryl, phenyl (C_1-C_{10})alkyl, and naphthyl (C_1-C_{10})alkyl group is independently unsubstituted or substituted by $(CH_2)_p$-OH or $(CH_2)_p$ NH_2, wherein p is an integer from 0 to 4 inclusive;~~

~~X_1, X_2 and X_3 independently of each other are N or C-R,~~ One of X_1, X_2 and X_3 is N and the other two of X_1, X_2 and X_3 are C-R, wherein R is selected from:

hydrogen;

(C_1-C_6)alkyl;

hydroxyl;

$(C_1$-$C_6)$alkoxy;

halo;

trifluoromethyl;

cyano;

nitro;

$S(O)_{n1}R_4$, wherein R_4 is as defined above;

$NR_{10}R_{11}$;

n_1 is an integer of from 0 to 2 inclusive;

R_{10} and R_{11} are the same or different, and are independently selected from

hydrogen;

$(C_1$-$C_6)$alkyl;

phenyl-$(C_1$-$C_{10})$alkyl; and

naphthyl-$(C_1$-$C_{10})$alkyl; or

R_{10} and R_{11} may be taken together with the nitrogen atom to which they are bonded to form a 5-membered or 6-membered ring containing carbon atoms, the nitrogen atom to which R_{10} and R_{11} are attached, and optionally a second heteroatom selected from O, S, N(H), and N$(C_1$-$C_{10})$alkyl,

~~wherein not more than two of the groups X_1, X_2, and X_3 simultaneously are a nitrogen atom;~~

n is an integer of from 0 to 8 inclusive;

Z is $C(R_{12})(R_{13})$;

Each R_{12} and R_{13} independently of each other are selected from:

hydrogen;

$(C_1$-$C_6)$alkyl;

trihalo$(C_1$-$C_6)$alkyl;

halo;

NH_2;

$(C_1$-$C_6)$alkylN(H);

$[(C_1$-$C_6)\text{alkyl}]_2N$, wherein each $(C_1$-$C_6)$alkyl moiety is the same or different;

OR_4;

SR_4; and

$C(=O)OR_4$, wherein R_4 is as defined above; or

R_{12} and R_{13} on the same carbon atom may be taken together with the carbon atom to which they are attached to form a carbonyl group; and

Z can contain 1 carbon-carbon double bond when two R_{12} groups are absent and n is an integer of from 2 to 8; and

Z can contain 2 carbon-carbon double bonds when four R_{12} groups are absent or three R_{12} and one R_{13} groups are absent and n is an integer of from 3 to 8; and

Z can contain 1 carbon-carbon triple bond when two each of R_{12} and R_{13} are absent and n is an integer of from 2 to 8; and

Z can contain 2 carbon-carbon triple bonds when four each of R_{12} and R_{13} are absent and n is an integer of from 4 to 8; and

One $C(R_{12})(R_{13})$ group in Z can be replaced with O, N(H), $N(C_1\text{-}C_6)$alkyl, S, S(O), or $S(O)_2$;

A is selected from:

phenyl;

an aromatic 5-membered or 6-membered monocyclic heterocycle comprising carbon atoms and from 1 to 4 heteroatoms selected from O, S, N(H), and $N\text{-}(C_1\text{-}C_{10})$alkyl;

a nonaromatic 5-membered or 6-membered monocycle comprising carbon atoms and from 0 to 4 heteroatoms selected from O, S, N(H), and $N\text{-}(C_1\text{-}C_{10})$alkyl;

naphthyl;

an aromatic 8-membered to 12-membered bicycle comprising two aromatic rings independently selected from 5-membered or 6-membered rings, wherein the rings may be the same or different and bonded or fused to each other, and wherein the bicycle comprises carbon atoms and from 1 to 6 hetero atoms selected from O, S, N(H), and $N\text{-}(C_1\text{-}C_{10})$alkyl;

an aromatic 8-membered to 12-membered bicycle comprising one aromatic 5-membered or 6-membered ring and one non-aromatic 5-membered or 6-membered ring, wherein the rings may be bonded or fused to each other, and

wherein the bicycle comprises carbon atoms and from 0 to 6 hetero atoms selected from O, S, N(H), and N-(C_1-C_{10})alkyl; and

a non-aromatic 8-membered to 12-membered bicycle comprising two non-aromatic rings independently selected from 5-membered or 6-membered rings, wherein the rings may be the same or different and bonded or fused to each other, and wherein the bicycle comprises carbon atoms and from 0 to 4 hetero atoms selected from O, S, N(H), and N-(C_1-C_{10})alkyl;

Each R_2 may be the same or different, and is independently selected from:

hydrogen;

(C_1-C_6)alkyl;

halo;

cyano;

nitro;

trihalo(C_1-C_6)alkyl;

$NR_{10}R_{11}$;

OR_{14};

SR_{14};

$S(O)R_{14}$;

$S(O)_2R_{14}$;

(C_1-C_6)acyl;

$(CH_2)_kNR_{10}R_{11}$;

$X_5(CH_2)_kNR_{10}R_{11}$;

$(CH_2)_kSO_2NR_{14}R_{15}$;

$X_5(CH_2)_kC(=O)OR_{14}$;

$(CH_2)_kC(=O)OR_{14}$;

$X_5(CH_2)_kC(=O)NR_{14}R_{15}$;

$(CH_2)_kC(=O)NR_{14}R_{15}$; and

X_6-R_{16};

X_5 is O, S, N(H), or N(C_1-C_6)alkyl;

k is an integer of from 0 and 3 inclusive;

R_{10} and R_{11} are as defined above;

R_{14} and R_{15} may be the same or different, and independently are hydrogen or (C_1-C_6)alkyl;

X_6 is a single bond, -CH_2-, O, or S, S(O), or $S(O)_2$;

R_{16} is selected from:

phenyl;

an aromatic 5-membered or 6-membered monocyclic heterocycle comprising carbon atoms and from 1 to 4 heteroatoms selected from O, S, N(H), and N-(C_1-C_{10})alkyl;

cyclopentyl;

cyclohexyl; and

a nonaromatic 5-membered or 6-membered monocyclic heterocycle comprising carbon atoms and from 1 to 3 heteroatoms selected from O, S, N(H), and N-(C_1-C_{10})alkyl;

wherein in R_{16} each phenyl, aromatic 5-membered or 6-membered, heterocyclic ring, cyclopentyl, cyclohexyl, and non-aromatic 5-membered or 6-membered heterocyclic ring group independently is unsubstituted or substituted with from 1 to 3 groups independently selected from (C_1-C_6)alkyl, halo, trihalo(C_1-C_6)alkyl, hydroxyl, (C_1-C_6)alkoxy, SH, (C_1-C_6)alkylthio, NH_2, (C_1-C_6)alkylN(H), [(C_1-C_6)alkyl]$_2$N, wherein each (C_1-C_6)alkyl moiety may be the same or different;

q is an integer of from 0 to 7 inclusive;

R_1 is a group selected from:

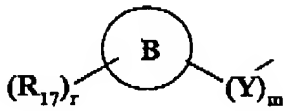
hydrogen;

(C_1-C_6)alkyl;

(C_3-C_6)alkenyl; and

(C_3-C_6)alkynyl,

wherein in R_1 each (C_1-C_6)alkyl, (C_3-C_6)alkenyl, and (C_3-C_6)alkynyl group is independently unsubstituted or substituted with from 1 to 3 groups independently selected from NH_2, (C_1-C_6)alkylN(H), [(C_1-C_6)alkyl]$_2$N, wherein each (C_1-C_6)alkyl moiety may be the same or different, (C_1-C_6)alkyl, cyano, trihalo(C_1-C_6)alkyl, C(=O)OR_4, OR_4, SR_4, wherein R_4 is as defined above, and a group of formula (1)



(1)

m is an integer of from 0 to 8 inclusive,

Y is $CR_{18}R_{19}$;

Each R_{18} and R_{19} independently of each other, is selected from:

hydrogen;

$(C_1\text{-}C_6)$alkyl;

phenyl;

trihalo$(C_1\text{-}C_6)$alkyl;

halo;

NH_2;

$(C_1\text{-}C_6)$alkylN(H);

$[(C_1\text{-}C_6)\text{alkyl}]_2N$, wherein each $(C_1\text{-}C_6)$alkyl moiety may be the same or different;

OR_4;

SR_4; and

$C(=O)OR_4$;

R_4 is as defined above;

Y can contain 1 carbon-carbon double bond when two R_{18} groups are absent and m is an integer of from 2 to 8; and

Y can contain 2 carbon-carbon double bonds when four R_{18} groups are absent or three R_{18} and one R_{19} groups are absent and m is an integer of from 3 to 8; and

Y can contain 1 carbon-carbon triple bond when two each of R_{18} and R_{19} are absent and m is an integer of from 2 to 8; and

Y can contain 2 carbon-carbon triple bonds when four each of R_{18} and R_{19} are absent and m is an integer of from 4 to 8; and

One $C(R_{18})(R_{19})$ group in Y can be replaced with O, N(H), $N(C_1\text{-}C_6)$alkyl, S, S(O), or $S(O)_2$;

B is a group selected from:

phenyl;

an aromatic 5-membered or 6-membered monocyclic heterocycle comprising carbon atoms and from 1 to 4 heteroatoms selected from O, S, N(H), and N-(C_1-C_{10})alkyl;

a nonaromatic 5-membered or 6-membered monocycle comprising carbon atoms and from 0 to 4 heteroatoms selected from O, S, N(H), and N-(C_1-C_{10})alkyl;

naphthyl;

an aromatic 8-membered to 12-membered bicycle comprising two aromatic rings independently selected from 5-membered or 6-membered rings, wherein the rings may be the same or different and bonded or fused to each other, and wherein the bicycle comprises carbon atoms and from 1 to 6 hetero atoms selected from O, S, N(H), and N-(C_1-C_{10})alkyl;

an aromatic 8-membered to 12-membered bicycle comprising one aromatic 5-membered or 6-membered ring and one non-aromatic 5-membered or 6-membered ring, wherein the rings may be bonded or fused to each other, and wherein the bicycle comprises carbon atoms and from 0 to 6 hetero atoms selected from O, S, N(H), and N-(C_1-C_{10})alkyl; and

a non-aromatic 8-membered to 12-membered bicycle comprising two non-aromatic rings independently selected from 5-membered or 6-membered rings, wherein the rings may be the same or different and bonded or fused to each other, and wherein the bicycle comprises carbon atoms and from 0 to 4 hetero atoms selected from O, S, N(H), and N-(C_1-C_{10})alkyl;

r is an integer of from 0 to 7 inclusive,

Each R_{17} may be the same or different and independently is selected from:

hydrogen;

(C_1-C_6)alkyl;

halo;

cyano;

nitro;

trihalo(C_1-C_6)alkyl;

$NR_{10}R_{11}$;

OR_{14};

SR_{14};

$S(O)R_{14}$;

$S(O)_2R_{14}$;

$(C_1\text{-}C_6)$acyl;

$(CH_2)_kNR_{10}R_{11}$;

$X_5(CH_2)_kNR_{10}R_{11}$;

$(CH_2)_kSO_2NR_{14}R_{15}$;

$X_5(CH_2)_kC(=O)OR_{14}$;

$(CH_2)_kC(=O)OR_{14}$;

$X_5(CH_2)_kC(=O)NR_{14}R_{15}$;

$(CH_2)_kC(=O)NR_{14}R_{15}$; and

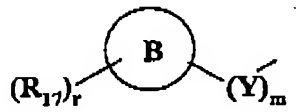
X_6-R_{16}, wherein X_5, k, R_{10}, R_{11}, R_{14}, R_{15}, X_6, and R_{16} are as defined above.

2 (original). The combination of Claim 1, wherein:

W_2 is $(C_1\text{-}C_6)$alkyl;

W_1 is O; and

$R_1$is a group of formula (1)



(1)

wherein Y, B, R_{17}, m, and r are as defined for Formula (A) in Claim 1.

3 (original). The combination of Claim 1, wherein the compound of Formula (A) is selected from:

4-{6-[3-(4-methoxy-phenyl-)-prop-1-ynyl]-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin -3-ylmethyl}-benzoic acid methyl ester;

4-[1-methyl-2,4-dioxo-6-(3-phenyl-prop-1-ynyl)-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoic acid;

4-{6-[3-(4-methoxy-phenyl-)-prop-1-ynyl]-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin -3-ylmethyl}-benzoic acid;

4-{6-[3-(4-methoxy-phenyl-)-prop-1-ynyl]-1-methyl-2,4-dioxo-1,4-dihydro-2H-pyrido[3,4-d]pyrimidin-3-ylmethyl}-benzoic acid;

4-[1-methyl-2,4-dioxo-6-(3-phenyl-prop-1-ynyl)-1,4-dihydro-2H-pyrido[3,4-d]pyrimidin-3-ylmethyl]-benzoic acid;

4-benzyl-7-(3-phenyl-prop-1-ynyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one;

4-benzyl-7-[3-(4-methoxy-phenyl)-prop-1-ynyl]-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one;

4-{7-[3-(4-methoxy-phenyl)-prop-1-ynyl]-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl}-benzoic acid methyl ester;

4-[5-oxo-7-(3-phenyl-prop-1-ynyl)-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl]-benzoic acid; and

4-(1-methyl-2,4-dioxo-6-(2-phenylethynyl)-1,4-dihydro-2H-quinazolin -3-ylmethyl)-benzoic acid;

or a pharmaceutically acceptable salt thereof, or an N-oxide thereof.

4 (original). The combination of Claim 1, wherein the compound of Formula (A) is selected from:

4-{6-[3-(4-methoxy-phenyl-)-prop-1-ynyl]-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin -3-ylmethyl}-benzoic acid methyl ester;

4-[1-methyl-2,4-dioxo-6-(3-phenyl-prop-1-ynyl)-1,4-dihydro-2H-quinazolin-3-ylmethyl]-benzoic acid;

4-{6-[3-(4-methoxy-phenyl-)-prop-1-ynyl]-1-methyl-2,4-dioxo-1,4-dihydro-2H-quinazolin -3-ylmethyl}-benzoic acid;

4-{6-[3-(4-methoxy-phenyl-)-prop-1-ynyl]-1-methyl-2,4-dioxo-1,4-dihydro-2H-pyrido[3,4-d]pyrimidin-3-ylmethyl}-benzoic acid;

4-[1-methyl-2,4-dioxo-6-(3-phenyl-prop-1-ynyl)-1,4-dihydro-2H-pyrido[3,4-d]pyrimidin-3-ylmethyl]-benzoic acid;

4-benzyl-7-(3-phenyl-prop-1-ynyl)-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one;

4-benzyl-7-[3-(4-methoxy-phenyl)-prop-1-ynyl]-4H-[1,2,4]triazolo[4,3-a]quinazolin-5-one;

4-{7-[3-(4-methoxy-phenyl)-prop-1-ynyl]-5-oxo-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl}-benzoic acid methyl ester;

4-[5-oxo-7-(3-phenyl-prop-1-ynyl)-5H-[1,2,4]triazolo[4,3-a]quinazolin-4-ylmethyl]-benzoic acid; and

4-(1-methyl-2,4-dioxo-6-(2-phenylethynyl)-1,4-dihydro-2H-quinazolin -3-ylmethyl)-benzoic acid.

5 (currently amended). A pharmaceutical composition, comprising a combination ~~of valdecoxib, or a pharmaceutically acceptable salt thereof, and an allosteric alkyne inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof,~~ according to claim 1 and a pharmaceutically acceptable carrier, diluent, or excipient.

6 (currently amended). A method of treating a disease or disorder selected from cartilage damage, inflammation, arthritis, and pain in a mammal, comprising administering to the mammal a therapeutically effective amount of a combination ~~of valdecoxib, or a pharmaceutically acceptable salt thereof, and an allosteric alkyne inhibitor of MMP-13, or a pharmaceutically acceptable salt thereof~~ according to claim 1.

7 (original). The method according to Claim 6, wherein the disease or disorder is rheumatoid arthritis.

8 (original). The method according to Claim 6, wherein the disease or disorder is osteoarthritis.

9 (original). The method according to Claim 6, wherein the disease or disorder is joint inflammation.

10 (original). The method according to Claim 6, wherein the pain is joint pain.